Remarks

Claims 1-6, 8 and 10 are currently pending. Claims 1-3 and 10 are amended herein. Support for the amendments to the claims may be found at least at the following pages: page 23, lines 5-9 (pharmaceutically acceptable salts); page 32, lines 27-32 (substituents in claims 1-3); page 33, lines 12-17 (substituents in claims 1-3); page 33, line 33 to page 34, line 2 (substituents in claims 1-3); page 35, line 23 onwards (claim 10); and pages 61-64 (claim 10). No new matter is added by these amendments.

Comments regarding Abstract

Applicants respectfully submit that the abstract was part of the international application that was submitted with this national stage filing. Further, Applicants respectfully point out that the abstract was acknowledged on the Notice of Missing Requirements mailed September 30, 2005. Applicants request that this rejection be withdrawn.

Section 112, First Paragraph Rejections

Claims 1-6, 8 and 10

Claims 1-6, 8 and 10 stand rejected under 35 U.S.C. § 112, first paragraph as not being enabled for solvates of the compound of formula I. The examiner asserts that applicants have not shown how one skilled in the art can arrive at a given solvate. In addition, the examiner asserts that arriving at a given solvate is not routine experimentation because it is unpredictable and one cannot make any solvate of a given compound. For the reasons stated below, Applicants respectfully disagree with this conclusion and instead assert that the claims in their current form are fully enabled commensurate with their scope.

The test for enablement is whether the disclosure, when filed, contained sufficient information to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. MPEP 2164.01.

> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

MPEP 2164.08 (emphasis added).

"In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure)." MPEP 2164.04. "[I]t is incumbent upon the Patent Office, whenever a rejection [for lack of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

In this case, the examiner has not met the initial burden of establishing a reasonable basis for doubting the enablement of the claimed invention. The examiner has not provided any evidence that one of ordinary skill in the art would not be able to form the claimed solvates without undue experimentation. The mere failure to include working examples that describe formation of solvates of the claimed compounds does not, as the examiner purports, mean that these forms of the compounds do not exist.

In general, the disclosure of the novel compounds of the claimed invention is more than sufficient to enable those having ordinary skill in the art to make and use the compounds as well as any solvates thereof. Applicants respectfully submit that one of ordinary skill in the art would be capable of making a solvate of the claimed compound without undue experimentation, especially given the level of ordinary skill in the art. Thus, it is applicants' position that the scope of enablement provided in the specification bears a more than "reasonable correlation" to the scope of claims 1-6, 8 and 10.

Moreover, contrary to the examiner's position, the specification specifically teaches solvates of the claimed compounds where the solvent adds across the imine bond of the pyrrolobenzodiazepine moiety. If the solvent is water or an alcohol, these solvates can be called the carbinolamine and carbinolamine ether forms of the pyrrolobenzodiazepine. (Specification at page 24, lines 20-29). Moreover, one of ordinary skill in the art would have known that any nucleophilic solvent, such as thiols and amines, is capable of forming such a solvate (specification at page 24, lines 30-33) and would have been able to make such solvates without undue experimentation.

Thus, applicants respectfully submit that the claims are fully enabled by the specification and request that the rejection be withdrawn.

Claim 10

In addition, claim 10 stands rejected under 35 U.S.C. § 112, first paragraph, as not enabled. The examiner asserts that the specification does not provide enablement for the treatment of proliferative diseases. Applicants have amended claim 10 to claim "[a] method of treatment of melanomas, or breast, renal, or lung cancer." Applicants respectfully submit that claim 10 as amended is enabled by the specification. At pages 61-64 of the specification, applicants show the results of biological assays on compounds of the present invention. The compounds were tested against cell lines for the following cancer types: breast, renal, lung and melanoma. The tested compounds inhibited the tested cancer cell lines as is shown by the IC_{50} data shown at pages 63-64 of the specification. Compounds of the present invention were also tested in a National Cancer Institute Hollow Fibre Assay (see pages 65-66 of the specification) and in standard subcutaneous xenograft models (see pages 66-67). Applicants respectfully submit that claim 10 as amended is enabled by the specification and request that the rejection be withdrawn.

Section 112, Second Paragraph Rejections

Claims 1-6, 8 and 10 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for various reasons. Applicants respectfully request that this rejection be withdrawn for the reasons discussed below. Applicants have amended claim 1 to use proper Markush form, to add the phrase "pharmaceutically acceptable" before the word "salt", to delete the phrase "chemically protected", to either delete the term "optionally substituted" or to define the substituents, and to replace "e.g." with "selected from the group consisting of". Applicants respectfully request that these rejections be withdrawn in light of the amendments to the claims.

Applicants disagree with the remaining rejections under § 112, second paragraph, and respectfully submit that the rejections are improper.

> The essential inquiry pertaining to [the § 112, second paragraph] requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

MPEP 2173.02.

The examiner asserts that the term "prodrug" is indefinite because the nature of prodrugs is not known and one cannot say which derivative results in a prodrug and which does not. Applicants respectfully submit that the examiner failed to take into account the teachings of

the prior art regarding prodrugs for pyrrolobenzodiazepines. The use of pyrrolobenzodiazepine prodrugs is known in the art as is discussed in the specification at page 26, line 34 through page 28, line 5. The synthesis and properties of pyrrolobenzodiazepine prodrugs are discussed in detail in WO 2000/12507, which is incorporated by reference in the specification on page 27. Thus, applicants respectfully submit that the use of the term "prodrug" does not render the claims indefinite and request that the rejection be withdrawn.

The examiner also asserts that the term "C_{3-20} heterocyclyl" is indefinite because a heterocyclic group necessarily requires the presence of heteroatoms and cannot be made solely of carbon atoms. The examiner asserts that it is not known how many atoms make up the ring, which atoms are present and what type of ring is intended. Applicants respectfully submit that the term "C_{3-20} heterocyclyl" is defined in the specification at page 7, line 9 to page 8, line 17. The definition makes it clear that the 3-20 refers to the total number of ring atoms with from 1 to 10 heteroatoms. (Page 7, lines 11-22). Applicants respectfully submit that the term "C_{3-20} heterocyclyl" is definite in light of the extensive definition in the specification and request that the rejection be withdrawn.

Finally, the examiner asserts that the term "C_{5-20} aryl" is indefinite because there are no C_5 or C_7 aryl groups. Applicants respectfully submit that this term is defined in the specification at page 8, line 19 to page 10, line 12. This definition makes it clear that the 5-20 refers to the total number of ring atoms, whether the ring atoms are carbon or heteroatoms. (Page 8, lines 19-29). Applicants respectfully submit that the term "C_{5-20} aryl" is definite in light of the extensive definition in the specification and request that the rejection be withdrawn.

Section 103 Rejection

Claims 1-6, 8 and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Thurston et al. (WO 2000/12508). The examiner cites Thurston et al. as teaching a generic group of compounds which embraces the claimed compounds.

Applicants respectfully submit that the Office Action fails to set forth a prima facie case of obviousness. "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP § 2143.03 *citing In re Royka*, 490 F.2d 981 (CCPA 1974). The patentability of a claim to a subgenus embraced by a prior art genus is analyzed no differently than any other claim under § 103. MPEP § 2144.08. The determination as to whether a *prima facie* case of obviousness exists should include analysis of the following factors: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; and (3) determine "the level of ordinary skill in the pertinent art. *Id.*

In the case of a prior art reference disclosing a genus such as this, the following findings are required to determine the scope and content of the prior art: (A) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus; (B) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus; (C) the predictability of the technology; and (D) the number of species encompassed by the genus taking into consideration all of the variables possible. *Id.* The Office Action has made no findings regarding the above criteria.

In addition, to establish a prima facie case of obviousness in a genus/subgenus chemical composition case, it is essential that a motivation or suggestion to make the claimed invention be found. *Id.* In order to determine whether such a motivatation exists, the following must be considered: (1) the size of the genus; (2) the express teachings of the reference; (3) the structural similarity between the genus and the subgenus and preferred or optimum species of the genus; (4) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus; and (5) the predictability of the technology. MPEP 2144.08. The Office Action made no findings on the above criteria.

The Office Action has set forth nothing more than the fact that Thurston et al. teaches a generic group of compounds which encompasses the claimed compounds. The Office Action does not provide any comparison because the prior art genus and the claimed genus nor does the Office Action provide any motivation to select the claimed genus from the broader prior art genus. Moreover, applicants respectfully submit that there is not motivation in Thurston et al. to select the claimed compounds from the broad genus disclosed therein. In addition, the specification shows, in the results of the biological assays given on pages 63 and 64, and the cytotoxicity studies given on page 67, that the compounds claimed in the present invention exhibit surprising activity against cancer cell lines as compared to other compounds disclosed in WO00/12508. Applicants therefore respectfully request that the rejection be withdrawn.

Double Patenting Rejection

Claims 1-6 stand rejected under the judicially created doctrine of non-statutory obviousness-type double patenting as being unpatentable over claims 1 and 40 of U.S. Patent 7,049,311 ("the '311 patent"). Applicants respectfully submit that the Office Action failed to set forth a proper rejection under the judicially created doctrine of non-statutory obviousness-type double patenting. "A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent

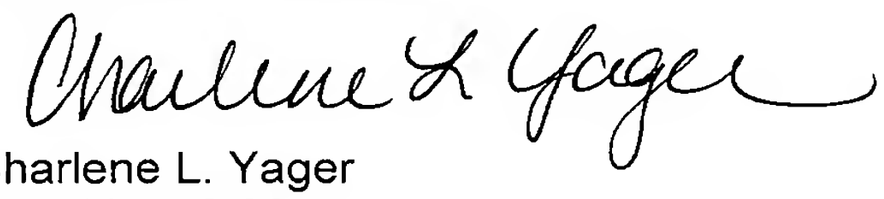
principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)." MPEP 804.

The Office Action sets forth none of the analysis required by an obviousness determination. The Office Action merely makes the statement "[o]ne of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the patent and arrive at the instant claims." (Office Action at 6). This unsupported statement is not sufficient to make a proper obviousness-type double patenting rejection. Moreover, applicants respectfully submit that the claims of the '311 patent provide no motivation to select the claimed compounds from the broad genus claimed therein. Applicants therefore request that the rejection be withdrawn.

CONCLUSION

In view of the remarks presented herein, it is believed that this application is now in condition for allowance. The Examiner is strongly encouraged to contact the undersigned at the phone number below should any issues remain with respect to the application. No fee is believed to be due in connection with this amendment and response. If this is in error, please charge the required fee to Deposit Account No. 50-0842.

Respectfully submitted,



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